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Application Number	09/989,725
Filing Date	NOVEMBER 20, 2001
First Named Inventor	AVI ASHKENAZI
Group/Art Unit	1647
Examiner Name	Fozia Hamud
Total Number of Pages in This Submission: 11	Attorney Docket Number: 39780-2730 P1C71

ENCLOSURES *(check all that apply)*

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SIGNATURE OF APPLICANT, ATTORNEY OR AGENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Hamud, Fozia
Avi ASHKENAZI, *et al.*	Art Unit: 1647
Application Serial No. 09/989,725	Confirmation No: 2364
Filed: November 20, 2001	Attorney's Docket No. 39780-2730 P1C71
For: **NUCLEIC ACIDS ENCODING PRO1375 POLYPEPTIDES**	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

On November 15, 2004, the Examiner made a final rejection to pending Claims 119-127, 129-132 and 134-138. A Notice of Appeal was filed on May 5, 2005 and an Appellants' Appeal Brief was filed October 3, 2005 and an amended Appeal Brief was filed May 30, 2006. An Examiner's Answer was mailed on August 8, 2006. A Reply brief was timely filed on October 10, 2006, since the USPTO was closed on Monday, October 9, 2006. An amended Examiner's Answer was mailed on November 3, 2006.

The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed.

ARGUMENTS

I. Priority

For the reasons outlined in their Appeal brief of May 30, 2006 and as discussed below, Appellants maintain that the instant application is entitled to the earlier priority date of U. S. Application Serial No. 60/144,758 filed **July 20, 1999**, for the claimed nucleic acids encoding PRO1375 polypeptides.

II. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Appellants submitted that patentable utility for the instantly claimed nucleic acids encoding PRO1375 polypeptides is based upon the data derived from the mixed leukocyte reaction (MLR) assay, as disclosed in Example 151 of the instant specification. Example 151 shows that PRO1375 tested positive in the mixed lymphocyte reaction (MLR) assay and therefore, is an immunoenhancer, which has utility in the treatment of conditions where the enhancement of an immune response would be beneficial (like increasing immunosurveillance in cancer). The Examiner has acknowledged the value of the MLR assay and that it is a well known assay in the art, based upon the teachings within U.S. Patent No. 5,817,306 and says that: "the MLR assay and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules in vitro that are useful for treating graft versus host disease (pages 6 and page 9 and page 17 of the Examiner's answer). The Examiner further acknowledged that the results obtained from these assays are generally predictive of their *in vivo* effectiveness (see column 12, lines 36-41 of U.S. Patent No. 5,817,306)."

However, the Examiner maintains the rejections to Claims 119-127, 129-132 and 134-138 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility. In summary, the Examiner basically concludes that "(t)he specification **fails to provide any data or evidence** of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion of the specification. The specification states that "positive increases over control are considered positive", however, this does not indicate that **statistical significance** must occur for determination of a positive result in the assay and therefore, the polypeptide in question may not alter the proliferation of stimulated T-lymphocytes to a significant extent...." (emphasis added; page 8, line 8 onwards of the

Examiner's Answer). The Examiner adds that "(t)here is insufficient data presented, as well as insufficient controls used, to conclude anything regarding the ability of the claimed polypeptide to be used in a substantial way to therapeutically (enhance) the immune response of an individual, and "further experimentation would be required to use the invention in this manner" (page 8, line 20 to page 9, line 2 of the Examiner's Answer). Regarding the Fong Declaration, the Examiner asserts that "the Fong declaration is not specific to the claimed protein, PRO1375. The Declaration provides no data related to the claimed protein, PRO1375. Furthermore, the opinion of Dr. Fong that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is ecpected to have the type of activity as that exhibited by IL-12" is not supported by any facts or eveidence of record. The references cited do not support this opinion and it is not clear how Dr. Fong arrived at this conclusion" (page 15, last lines to page 16, line 10 of the Examiner's Answer).

Appellants disagree with each of the Examiner's arguments for the reasons detailed below.

Arguments:

Appellants assertion for utility for the nucleic acids encoding PRO1375 polypeptides is based on a positive result in the MLR assay, which the Examiner has acknowledged as being a well known assay in the art, and which is valuable for identifying immunostimulants (also referred to as immune enhancers) *in vitro*. Such molecules are useful, in the treatment of viral infections or cancer, for example, or for treating diseases like graft versus host disease. Based on their identification of PRO1375 as an immunosuppressive molecule, one skilled in the art would find it credible that PRO1375 is useful in the treatment of conditions where the enhancement of an immune response would be beneficial. The specification expressly states that, in the MLR assay, positive increases over control, especially increases of greater than or equal to 180% is preferred. Yet the Examiner asserts that "further experimentation would be required to use the invention in this manner."

Appellants respectfully disagree. Regarding the need for values or data for the proteins tested in the assay or "statistics" for the values measured, the remarks are a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a drug based on the immunoenhancer activity of PRO1375, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an

application for a new immunoenhancer drug, will indeed ask for actual numerical data, statistical analysis, and other specific information before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.[1] Indeed, in *Nelson v. Bowler,*[2] the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to the instant utility as well. The identification of a compound as an immunoenhacer should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

The MLR assay described herein is a comparative one, meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. Useful information is obtained when a relative differences are observed, and this is routine in biological testing. All that is important for utility is that the difference is significant and Appellants expressly assert that the observed difference for PRO1375 is significant. For instance, the specification expressly states that, in the instant MLR assay, positive increases over control, especially increases of greater than or equal to 180% is preferred and that PRO1375 tested positive in this assay. The Examiner seems to focus on exactly how much higher (*i.e.,* requiring Applicants to provide "relative or absolute levels" and statistical analyses), but Applicants submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful.

Appellants further respectfully remind the Examiner that an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "**unless there is a reason for one skilled in threat to question the objective truth of the statement of utility or its scope**." (emphasis added) *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974). *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977). Compliance with 35 U.S.C.

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[1] *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994).

[2] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

§101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Examiner has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." (emphasis added) *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Appellant to provide rebuttal evidence. *Id.* The Examiner has not cited a single reference that would show that one of ordinary skill in the art would reasonably doubt the asserted utility. Accordingly, a proper prima facie case has not been made in this instance and the burden to rebut this rejection has not entirely shifted to the Appellants.

Yet, Appellants provided the Fong Declaration to explain how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs). In fact, the Fong Declaration detailed the state of the art, at the time of filing, in the field of immunostimulation/ suppression and provided art accepted examples of the usefulness for such immunostimulant molecules. Based on these teachings, it is more likely than not that one skilled in the art, to a reasonable probability, would believe that the claimed polypeptide is useful as an immunostimulant. Further, the present application discloses this utility for PRO1375 such that one of skill in the art would know exactly how to use the claimed polypeptides as immunostimulants, for instance, for immunesurveillance in diseases like cancer, without any undue experimentation. The specification also provides detailed guidance on how to identify and make nucleic acid variants encoding PRO1375 polypeptides. The Examiner, on the other hand, has not met the initial burden of establishing a *prima facie* case for lack of utility. Thus, Appellants believe that this rejection of Claims 119-127, 129-132 and 134-138 should be withdrawn.

III. *Claim Rejections Under 35 U.S.C. §112, First Paragraph- Written Description*

Applicants maintain that the specification provides ample guidance to allow the skilled artisan to identify those polypeptide variants which meet the recitations of Claims 119-124, 127, 132 including a detailed protocol for the MLR assay. The specification also provides detailed guidance as to how to identify and make nucleic acids having at least 80% sequence identity to the nucleic acid encoding the polypeptide of PRO1375 (SEQ ID NO:418) or the nucleic acid of SEQ ID NO: 417. Accordingly, one of ordinary skill in the art would know that Appellants had possession of the recited nucleic acid variants.

Claims 119-124, 127, and132 recite the functional recitation "wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction." Accordingly, coupled with the general knowledge available in the art at the time of the invention, Appellants submit that the specification provides ample written support for the claimed nucleic acids in the specification.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[3, 4] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[5] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[6, 7]

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[3] *In re Kaslow*, 707 F.2d 1366, 1374, 212 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983).

[4] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991).

[5] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 U.S.P.Q.2d at 1116.

[6] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[7] *See also* M.P.E..P. §2163 II(A).

In *Environmental Designs, Ltd. v. Union Oil Co.*,[8] the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[9] Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[10, 11]

B. The Disclosure Provides Sufficient Written Description for the Claimed Invention

Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO:418 and nucleic acid sequence of SEQ ID NO: 417. The Examiner has acknowledged that nucleic acids comprising the sequence set forth in SEQ ID NO:417 meet the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of nucleic acids with at least 80% nucleic acid sequence identity to the nucleic acid of SEQ ID NO:417 or that nucleic acid encoding SEQ ID NO:418, which polypeptides possess the functional property of inducing proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction, would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Appellants submit that, as discussed above, whether a specification shows that Appellants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teachings provided by the specification. The inventor is not required to describe every single detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains.

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[8] 713 F.2d 693, 696, 218 U.S.P.Q. 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[9] *See also* M.P.E.P. §2141.03.

[10] *Ex parte Hiyamizu*, 10 U.S.P.Q.2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[11] *See also* M.P.E.P. §2141.03.

The present invention is from the field of recombinant DNA technology. In addition, the claims recite that the polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction. It is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field. Accordingly, the teachings imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

Example 151 of the present application provides step-by-step guidelines and protocols for the identifying polypeptides with MLR activity. By following the disclosure in the specification, one skilled in the art could easily test whether a variant nucleic acid that encodes PRO1375 polypeptide would induce proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction. Nucleic acid variants are described on page 308, line 7 onwards. The specification further describes methods for the determination of percent identity between two nucleic acid sequences (page 309, line 1, to page 311). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether a variant nucleic acid encoding PRO1375 sequence falls within the parameters of the claimed invention. Once such an nucleic acid sequence is identified, the specification sets forth methods for making amino acid sequences (see page 371, line 6, to page 375, line 9) and methods of preparing the PRO polypeptides (see page 375, line 11 and onward).

Appellants have recited structural features, namely, 80% nucleic acid identity to the nucleic acid encoding SEQ ID NO:418, which are common to the genus. Appellants have also provided guidance as to how to make the recited variant nucleic acids. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

In view of the above, Appellants respectfully request reconsideration and reversal of the written description rejection of Claims 119-124, 127 and 132 under 35 U.S.C. §112, first paragraph.

IV. *Claim Rejections Under 35 U.S.C. §102*

Appellants maintain that, based on an effective filing date of **July 20, 1999** for the instant application, which is over six months before the publication date of WO00/18904, WO00/00610,

WO00/00506, and at least one month before the publication date of WO99/63088, neither of the cited references are prior art. Similarly, the effective filing date of **July 20, 1999** for the instant application is over six months before the publication date of EP1130094, which therefore, is also not prior art. Appellants maintain that this rejection should be withdrawn.

CONCLUSION

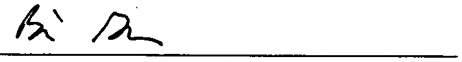
For the reasons given above, Appellants submit that the MLR assay disclosed in Example 151 of the specification provides at least one patentable utility for the nucleic acids encoding PRO1375 polypeptides, and that one of ordinary skill in the art would understand how to use the claimed nucleic acids, for example, in making polypeptides that are useful in therapeutic applications where enhancement of an immune response is beneficial, such as the treatment of viral infections or cancer. Therefore, Claims 119-127, 129-132 and 134-138 meet the requirements of 35 USC §101 and 35 USC §112, first paragraph. Further, this patentable utility for the claimed polypeptides was first disclosed in U.S. Provisional Application Serial No. 60/144,758, filed on July 20, 1999, priority to which is properly claimed in the instant application. Accordingly, the instant application has an effective priority date of July 20, 1999, and therefore neither WO00/18904, (published June/2000); WO99/63088, (published September/1999); WO00/00610, (published June/2000); WO00/00506, (published June/2000) nor EP1130094, (published September/2001) are prior art and they do not anticipate the claims under 35 USC §102(a) or (b).

Accordingly, reversal of all the rejections of Claims 119-127, 129-132 and 134-138 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C71**).

Respectfully submitted,

Date: January 3, 2007



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